Article

Clinical application of recombinant human bone morphogenetic protein in cats and dogs: A review of 13 cases

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Abstract — Databases (2001–2008) for cases in which recombinant bone morphogenetic protein (rhBMP) was used to aid in management of orthopedic disease were reviewed and cases were categorized as non-unions, delayed unions, and cases expected to heal with difficulty. If follow-up in the medical record was < 6 mo for live animals, owners were surveyed by telephone. Thirteen cases (11 dogs, 2 cats) were identified; OP-1 (rhBMP-7) was used in 3 cases and INFUSE (rhBMP-2) in 10. Mean time from injury to rhBMP use for non- and delayed union cases was 156 d; mean time from rhBMP use to radiographic healing was 101 d. No systemic side effects were reported. All patients achieved clinical and radiographic bone union following rhBMP administration. Recombinant human BMP was used in 13 veterinary patients to successfully achieve bone union without serious deleterious effects in a variety of clinical applications.

Résumé — Application clinique de la protéine morphogénétique osseuse recombinante humaine chez les chats et les chiens : examen de 13 cas. Les bases de données (2001–2008) de cas où la protéine morphogénétique osseuse recombinante humaine (rhBMP) a été utilisée pour faciliter la gestion des problèmes orthopédiques ont été évaluées et les cas ont été classés comme des non-unions, des unions retardées et des cas avec un pronostic de guérison difficile. Si le suivi du dossier médical était de < 6 mois pour les animaux vivants, on a procédé à une enquête téléphonique auprès des propriétaires. Treize cas (11 chiens, 2 chats) ont été identifiés; OP-1 (rhBMP-7) a été utilisé dans 3 cas et INFUSE (rhBMP-2) dans 10 cas. Le délai moyen entre la blessure et l'utilisation de rhBMP pour les cas de non-union et d'union retardée était de 156 jours; le délai moyen entre l'utilisation de rhBMP jusqu'à la guérison radiographique était de 101 jours. Aucun effet secondaire systémique n'a été signalé. Tous les patients ont obtenu l'union clinique et radiographique de l'os après l'administration de rhBMP. La protéine morphogénétique osseuse recombinante humaine a été utilisée chez 13 patients vétérinaires afin d'obtenir une union osseuse réussie sans effets délétères graves dans diverses applications cliniques.

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Introduction

Advancement in surgical technique, facilities, and technology has brought about an improvement in a veterinary surgeon's ability to treat complex orthopedic diseases. Most companion animal fractures heal successfully; however, complications and failures do occur. Recognition of difficult cases at the onset of treatment allows therapeutic modulations to increase the chance of a successful outcome. Bone morphogenetic proteins (BMPs) are signaling molecules that can initiate *de novo* bone formation. In recent years, commercially available BMP products, rhBMP-2 (INFUSE™ Bone Graft; Medtronic, Minneapolis, Minnesota, USA) and rhBMP-7 (OP-1 Implant; Stryker Biotech, Hopkinton, Massachusetts, USA) have been used in human orthopedics to enhance bone formation in spinal fusions and non-union long bone fractures (1). The use of rhBMP products by orthopedic surgeons has been limited by their relatively high cost (2).

In most cases in veterinary medicine, fresh autologous cancellous bone graft (ACBG) is more than adequate to enhance bone healing. However, if ACBG is unavailable or a fracture results in non-union despite grafting with ACBG, the extra label use of BMP may be beneficial. There are reports of the use of rhBMP-2 to treat dogs with delayed unions (3,4), mandibular defects (5,6), and radial atrophy (7). Another paper reported the use of a nonglycosylated BMP-2/fibrin gel product to treat delayed unions in cats and dogs (8). However the use of rhBMP-7/OP-1 has not been reported in cats or dogs. The objective of this report is to describe a series of cases in which rhBMP-2 or rhBMP-7 was used as an adjunct for bone healing.

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Materials and methods

Medical record review

The rhBMP products were obtained for extra label use with the owners' informed consent in 13 orthopedic cases (11 dogs, 2 cats) to aid in bone healing. Details of each case were obtained from reviewing medical records from the specialty surgical practices where the authors had been employed between 2001 and 2008. For cases in which follow-up was inadequate after application of the rhBMP (n = 5), the pets' owners or referring veterinarians (rDVM) were contacted by telephone. A list of standardized questions regarding use of the fractured limb, pet activity, and overall owner satisfaction was used to assess final outcomes in these cases.

Use of rhBMP

The rhBMP was used to treat delayed or non-union fractures and some cases in which healing was expected to be compromised. Fractures were classified as delayed or non-unions if the fracture had not reached radiographic union by the expected time as previously reported (9), if there was no, or non-bridging callus formation, and if the medical record stated a clinical diagnosis of delayed or non-union. Cases in which healing was expected to be compromised were defined as those with variables that can affect fracture healing and the need for grafting of some kind was deemed necessary by the surgeon.

The rhBMP-7 was used in 3 cases (1, 4, and 7) and rhBMP-2 was used in the remaining cases. The OP-1 implant is supplied as a lyophilized powder (3.5 mg rhBMP-7) mixed with purified Type I bovine collagen (1 g) that is resuspended in 2.0 mL of sterile 0.9% sodium chloride (NaCl). The product is mixed with a sterile curette for ~ 2 min while it expands to a maximum volume. This OP-1 paste was used promptly after reconstituting with saline. The INFUSE product contains rhBMP-2 (4.2 mg) that is resuspended in 2.8 mL of sterile water (final concentration of 1.5 mg/mL) and applied to an absorbable collagen sponge (ACS). The protein must adsorb to the ACS for a minimum of 15 min before it is placed in the fracture site. Sponges of purified Type I bovine collagen can also be purchased separately (Helistat; Integra LifeSciences Corp., Plainsboro, New Jersey, USA). The rhBMP-2/ACS INFUSE product was used in all cases in which rhBMP-2 was used except 1 in which demineralized bone matrix was used as the carrier (case 6).

The fracture sites were completely debrided of fibrous, necrotic, or sclerotic tissue and the fracture fragments were completely stabilized using a variety of implants as described under the individual cases. Complete hemostasis was achieved before product placement to ensure the material stayed at the surgical site. Both products were applied directly to the prepared osseous tissue at the site of desired bone formation, i.e., the primary fracture gap. The use of irrigation and suction was minimized after product placement to maintain the product at the desired site. The soft tissues were closed around the surgical site with the BMP product, and the skin incision was sutured to close. No drains were used at any of the surgical sites to prevent loss of the protein.

Radiographs were taken immediately after the surgery to place the rhBMP to assess fracture reduction and the method of fixation. Radiographs were repeated every 2 to 6 wk until there was radiographic healing, greater than 2 cortices with bridging callus on orthogonal radiographs.

Results

Overall

Mean time to follow-up for all cases was 427 d (range: 48 to 1371 d). All owners reported good to excellent limb use and mean eventual owner satisfaction was 9.7/10 (10 = completely satisfied). No owner reported any additional surgeries to the limb following radiographic union. Two pets were euthanized shortly after radiographic union was confirmed for reasons unrelated to their original diseases; 1 for a pathological fracture secondary to osteosarcoma in an unrelated limb and 1 for urinary obstruction secondary to a pubic malunion. A description of the 13 clinical cases follows. The details of each case are summarized in Table 1.

Non-unions and delayed unions

Eight cases, 7 canine and 1 feline, were classified as non-unions or delayed unions. There were 3 neutered males (MN), 2 intact males (MI), and 2 spayed female (FS) dogs; the cat was MN. The mean age of the dogs was 7.1 y (range: 2 to 13.25 y) and mean weight was 32.27 kg (range: 3.1 to 92.2 kg). Of the delayed union cases, 2 dogs (cases 4 and 7) were treated with OP-1 and 3 dogs (cases 5, 6, and 8) were treated with rhBMP-2, ACS was the carrier in cases 5 and 8. The dog in case 6 was the only dog treated with rhBMP-2 adsorbed to an alternate carrier. The resuspended protein was mixed with 1 cc of canine demineralized bone matrix (DBM; Veterinary Transplant Services, Kent, Washington, USA).

The mean time from original injury to diagnosis of a delayed union and the decision for rhBMP use was 152 d (range: 71 to 270 d). For these animals, the mean time from administration of rhBMP to diagnosis of a radiographic union was 105.8 d (range: 56 to 135 d). The mean time from the original injury to the diagnosis of a non-union and placement of the rhBMP was 207 d (range: 128 to 273 d). The mean time from rhBMP placement to radiographic union was 77.6 d (range: 69 to 84 d). Of the non-union cases, 1 dog (case 1) was treated with OP-1 (1.17 mg) and the other dogs (cases 2 and 3) were each treated with rhBMP-2/ACS (0.4 mg of rhBMP-2).

Dogs 1 and 2 were originally presented for polytrauma with multiple orthopedic injuries. The open, radius-ulna fracture in case 1 ended in a non-union in part from injuries that included a contralateral open humeral condylar fracture. The fracture was deemed irreparable and treated by forelimb amputation, which resulted in greater use of the remaining thoracic limb. Healing of the humeral fracture in case 2 was affected by an ipsilateral femoral fracture stabilized with an interlocking nail. Initial stabilization of the radius-ulna fracture in case 1 and the humeral fracture in case 2 was accomplished with external skeletal fixation (ESF). The ESF in case 2 was applied after open reduction and interfragmentary compression with full cerclage wires and a screw placed in lag fashion. The lengthy courses of surgical management that included multiple implant modifications in both of these cases were complicated by osteomyelitis. In both

Table 1. Case information for all 13 cases[a] in which rhBMP was used to aid in bony union

Case	Indication for rhBMP	Breed	Age (y)	Sex	Original injury	Original fixation	Final fixation (where rhBMP used)	Time from original injury to rhBMP (d)	Time from rhMBP to radiographic healing (d)	Type of rhBMP
1	Non-union	German shepherd	5	MN	Open radius/ulna fracture	Hybrid ring fixator	Trans-articular type II ESF	220	77	OP-1
2	Non-union	Collie	7	FS	Comminuted humeral fracture	Modified type 1–2 hybrid ESF IM pin tie in	Interlocking nail	273	72	BMP-2
3	Non-union	Yorkshire terrier	5	FS	Metacarpal fractures (2–5)	Spoon splint	Pin fixation of metacarpals; pan-carpal arthrodesis	128	84	BMP-2
4	Delayed union	Manx	8	MN	Mid tibia/fibula oblique fracture	Interlocking nail	Dynamic compression plate	71	127	OP-1
5	Delayed union	Mastiff	7	MN	Comminuted femur fracture	IM pin and dynamic compression plate	Dynamic compression plate	141	135	BMP-2
6	Delayed union	Labrador retriever	13	MI	Metacarpal fracture (3–5)	Bar splint	Bar splint	79	92	BMP-2
7	Delayed union	Australian shepherd	2	MN	Comminuted femur fracture	Interlocking nail	Interlocking nail	270	56	OP-1
8	Delayed union	Saluki	11	MI	Carpal hyperextension	Hybrid dynamic compression arthrodesis plate (not all screws locking)	Hybrid dynamic compression plate (new plate with all screws locking)	199	119	BMP-2
9	Expected difficulties	Labrador retriever	4.5	MN	Spiral tibial fracture	Hybrid ring fixator	Revised hybrid ring fixator	44	107	BMP-2
10	Expected difficulties	German shepherd	12	FS	TPLO failure	Type 1 ESF; reapplication TPLO plate; tension band	TPLO plate	8	296	BMP-2
11	Expected difficulties	Cocker spaniel	11	FS	Comminuted tibia/tarsal fracture	Ring fixator tarsal arthrodesis	Ring fixator	13	48	BMP-2
12	Expected difficulties	Domestic shorthair	2	MI	Comminuted humeral fracture	Dynamic compression plate — buttress	Dynamic compression plate — buttress	3	83	BMP-2
13	Expected difficulties	Labrador retriever	2	FI	Bilateral comminuted fracture	Interlocking nail	Interlocking nail	5	46	BMP-2

[a] All cases reached radiographic union after administration of rhBMP. No systemic side-effects were reported for any cases after application of rhBMP.
BMP — bone morphogenetic protein, rhBMP — recombinant BMP; MN — male, neutered; MI — male, intact; FS — female, spayed; FI — female, intact; TPLO — tibial plateau leveling osteotomy, ESF — external skeletal fixation, IM — intramedullary.

cases the osteomyelitis resolved, based on serial radiographic assessments after definitive stabilization, rhBMP placement, and continued antibiotic therapy.

The radius-ulna fracture in case 1 was re-stabilized 10 wk after the initial surgery with a type II ESF that included fixation pins in the distal humerus to increase bone purchase for the proximal segment. The location of the humeral pin was changed and fracture site grafted with one-third of an OP-1 implant containing about 1.17 mg of OP-1 12 wk later. The fracture was clinically and radiographically healed 77 d after placement of the BMP, and all implants were removed.

During replacement of loose pins and fracture debridement in case 2, 18 wk after the initial surgery, an autologous bone marrow aspirate was mixed with platelet rich plasma (PRP) and injected into the fracture site. There was still no evidence of bone healing 10 wk later despite the autologous marrow and PRP graft. Thirty weeks after the initial surgery, the ESF and intramedullary (IM) pin were removed from the humerus, the fracture fragment ends were extensively debrided and stabilized with an interlocking nail. An ACS loaded with 0.4 mg of rhBMP-2 (0.5 mg/mL solution) was wrapped around the freshened ends of the fracture fragments (Figure 1). Osseous

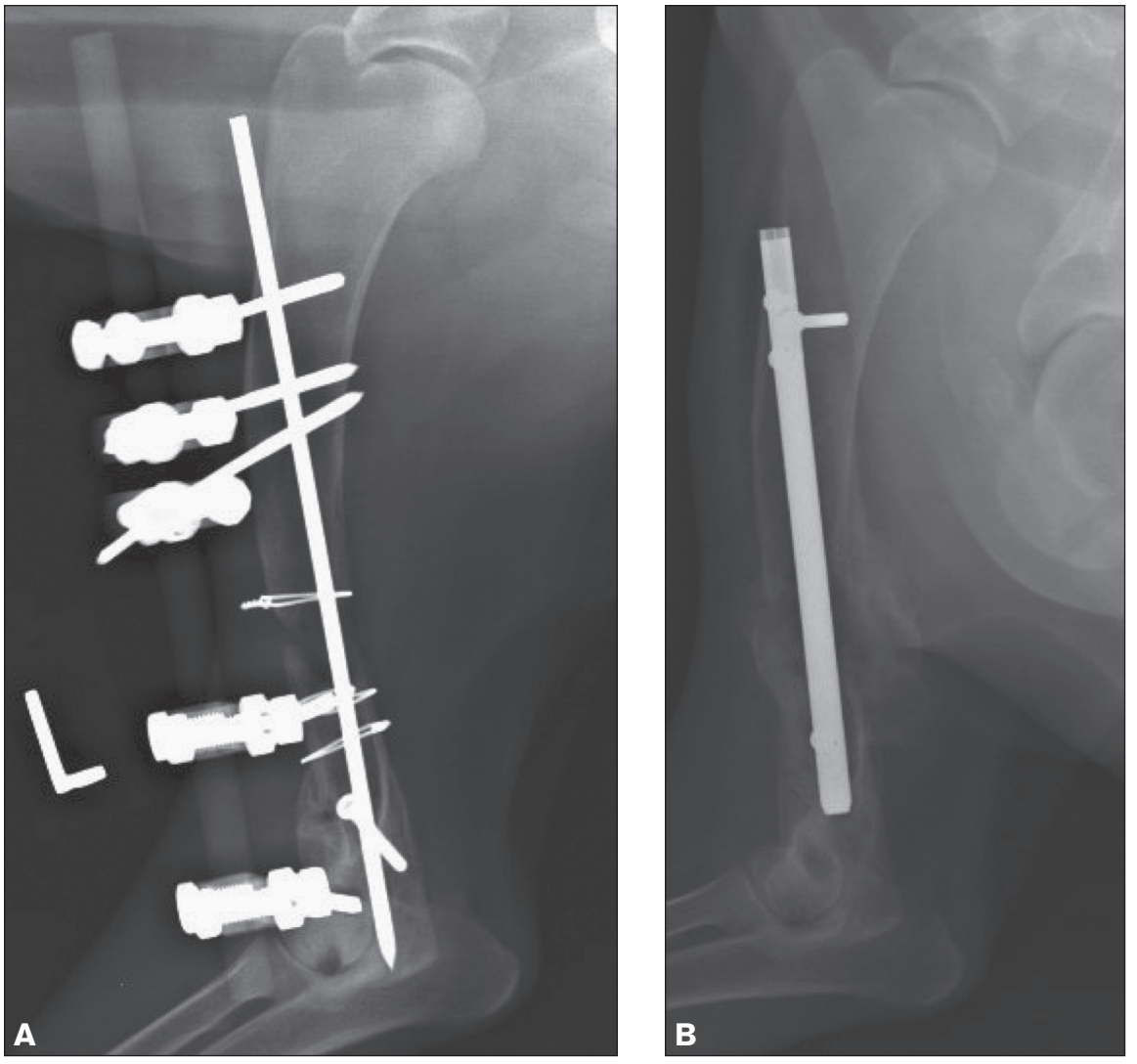

Figure 1. A. Case 2 – humeral non-union with external skeletal fixation (ESF) 270 d after the initial injury. B. Case 2 – 7 wk after the image shown in A. Fracture management involved replacement of ESF with interlocking nail (ILN) and application of 0.4 mg rhBMP-2/ACS (3 wk after ILN) promoting large, bridging callus formation.

bridging of the fracture site was seen on radiographs taken 72 d after placing the nail and BMP.

Case 3 was presented with fractures of metacarpal (MC) bones II-V that resulted in atrophic non-union of all MC bones after stabilization for 6 mo with a spoon splint. The non-union fractures were treated by intramedullary 0.035-in Kirschner wires in metacarpal bones II, III, and V. A pancarpal arthrodesis was also performed with the plate applied distally to metacarpal bone IV. The arthrodesis and fracture sites were augmented with both autogenous corticocancellous bone graft and 0.4 mg of rhBMP-2 (0.5 mg/mL solution) on an ACS. The fractures and arthrodesis achieved radiographic union 69 d after surgical treatment.

The fractures in cases 4 and 7 were originally stabilized with interlocking nails. Case 4 was a Manx cat that had an interlocking nail used to stabilize a closed oblique tibial fracture 3 y after an ipsilateral pantarsal arthrodesis. The nail was removed when a fracture developed distal to the nail, and a bone plate was used to stabilize the tibia. The plate loosened after bone loss developed from osteomyelitis. Loose screws were replaced and full cerclage wires that encompassed the plate were used to stabilize the fracture and 1/3 of an OP-1 implant (1.17 mg OP-1) was placed around the fracture lines 8 wk after the initial surgery. Eight weeks later some callus formation was noted on radiographs, which progressed to a complete bridging callus in another 8 wk. In case 7, a 2-year-old dog with a comminuted femoral fracture from vehicular trauma was treated with fresh autogenous cancellous bone graft and stabilized with an interlocking intramedullary nail. The dog used the limb well until slipping on ice 9 mo later. Radiographs showed atrophic non-union and broken screws in the proximal end of the nail. The broken screws were replaced by locking bolts and the fracture gap was supplemented with a full OP-1 implant containing 3.5 mg of OP-1. The dog used the limb immediately after surgery and a large bridging mineralized callus was seen on radiographs taken 8 wk later.

The delayed union of the fractures in cases 5 and 8 resulted from failure of the bone plates used for initial fracture stabilization

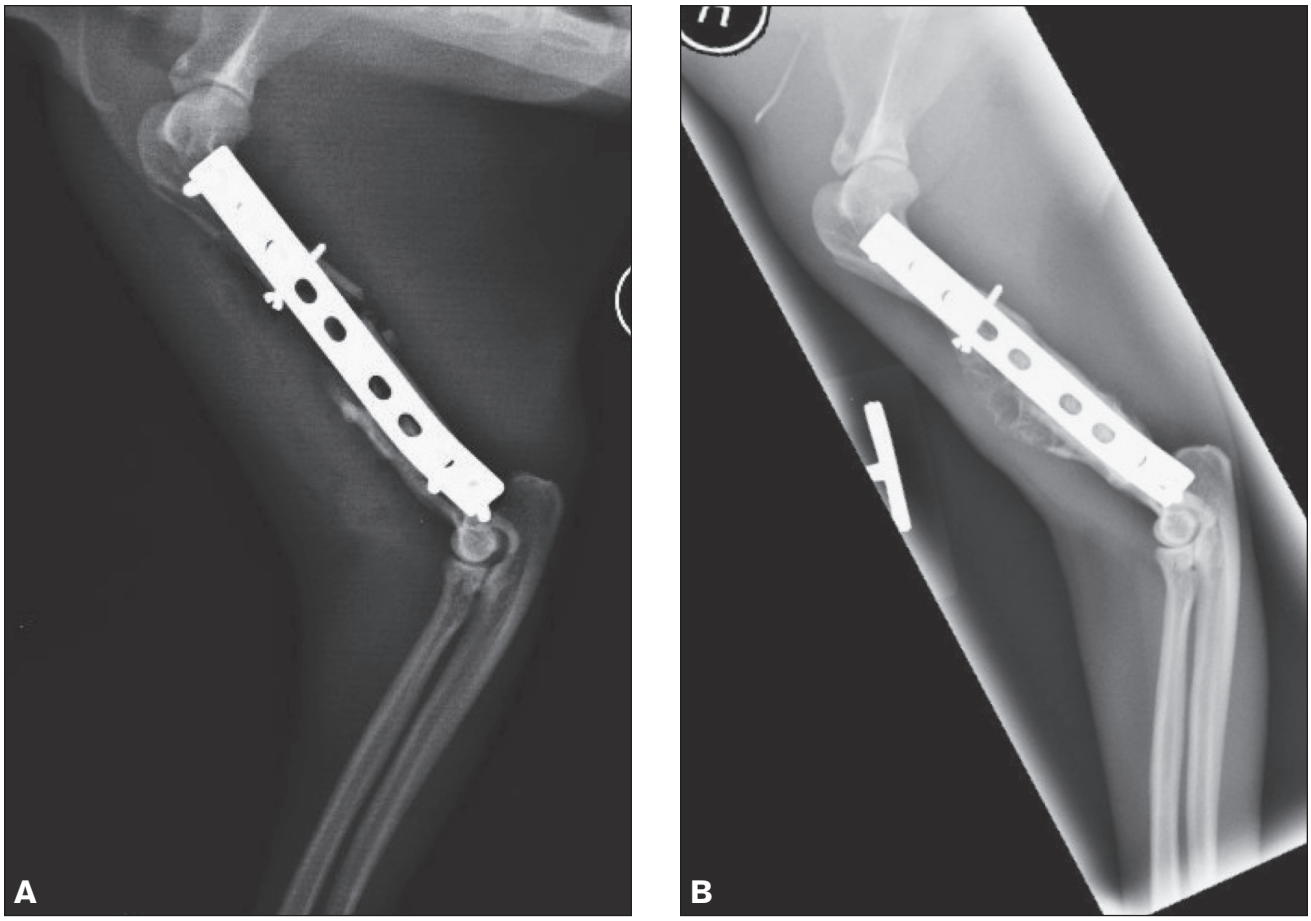

Figure 2. A. Case 12 – A large gap in the caudal cortex following fracture reduction and stabilization prompted the use of 0.4 mg rhBMP-2/ACS in fracture healing augmentation. B. A large bridging and remodeled callus is visible 12 wk after surgery.

in 2 different clinical circumstances. An obese 7-year-old Mastiff in case 5 was hit by a car and sustained left acetabular and comminuted mid-diaphyseal femoral fractures. The femoral fracture was stabilized with a 4.5 mm dynamic compression (DC) plate-rod combination augmented with fresh autogenous cancellous and morsellized cortical bone graft. The dog's limb function was limited by the medically managed acetabular fracture and the presence of severe osteoarthritis in both stifles from chronic cranial cruciate ligament rupture; he had conscious proprioceptive deficits in the affected limb as well. Minimal callus formation and bone resorption at the fracture gap were seen on serial radiographs taken over 19 wk after surgery. The fracture was revised by removing the IM pin, replacing 4 loose screws in the plate, and implanting an ACS with 0.4 mg rhBMP-2 (0.5 mg/mL solution) at the fracture site. There was radiographic evidence of complete healing of the fracture 84 d later. However the dog continued to have limited limb use and conscious proprioceptive deficits, so the owners requested humane euthanasia 3 mo later.

The dog in case 8 had a pancarpal arthrodesis performed using standard technique with bone plating, cartilage debridement, and fresh autogenous corticocancellous bone graft to treat a subacute carpal hyperextension injury. Three months after surgery, the plate broke and the arthrodesis failed despite having been supported with external coaptation. A new bone plate was placed on the carpus and the arthrodesis was augmented with fresh autogenous corticocancellous bone graft and an ACS with 0.4 mg of a 0.5 mg/mL rhBMP-2 solution. External coaptation with a palmar splint was used for 8 wk after the second surgery. There was successful fusion of the arthrodesis 119 d after the revision surgery without any further complications.

The 13-year-old Labrador retriever dog in case 6 sustained carpal and tarsal lacerations and grade II open fractures of metacarpal bones 3, 4, and 5 from a snowplow accident. The wounds were medically managed with a bar splint, regular bandage changes, and oral antibiotics. There was resorption of the fracture fragments and no callus formation on radiographs taken every 3 to 4 wk after the injury. After 11 wk, 0.4 mg of rhBMP-2 of a 0.5 mg/mL solution mixed with 1 cc of demineralized bone matrix was injected into the MC III and IV fracture gaps through small stab incisions using fluoroscopic guidance. Complete bone union of all fractures was found by physical and radiographic examinations 92 d after BMP administration.

Compromised healing

There were 5 cases, 4 canines and 1 feline, in which rhBMP was used early in the surgical treatment (mean time to rhBMP treatment 14 d; range: 3 to 44 d) because it was suspected that healing might be compromised. The mean age of these animals was 6.3 y (range: 2 to 12 y) and their mean weight was 26.45 kg (range: 8.6 to 38.4 kg). There were 3 female dogs,

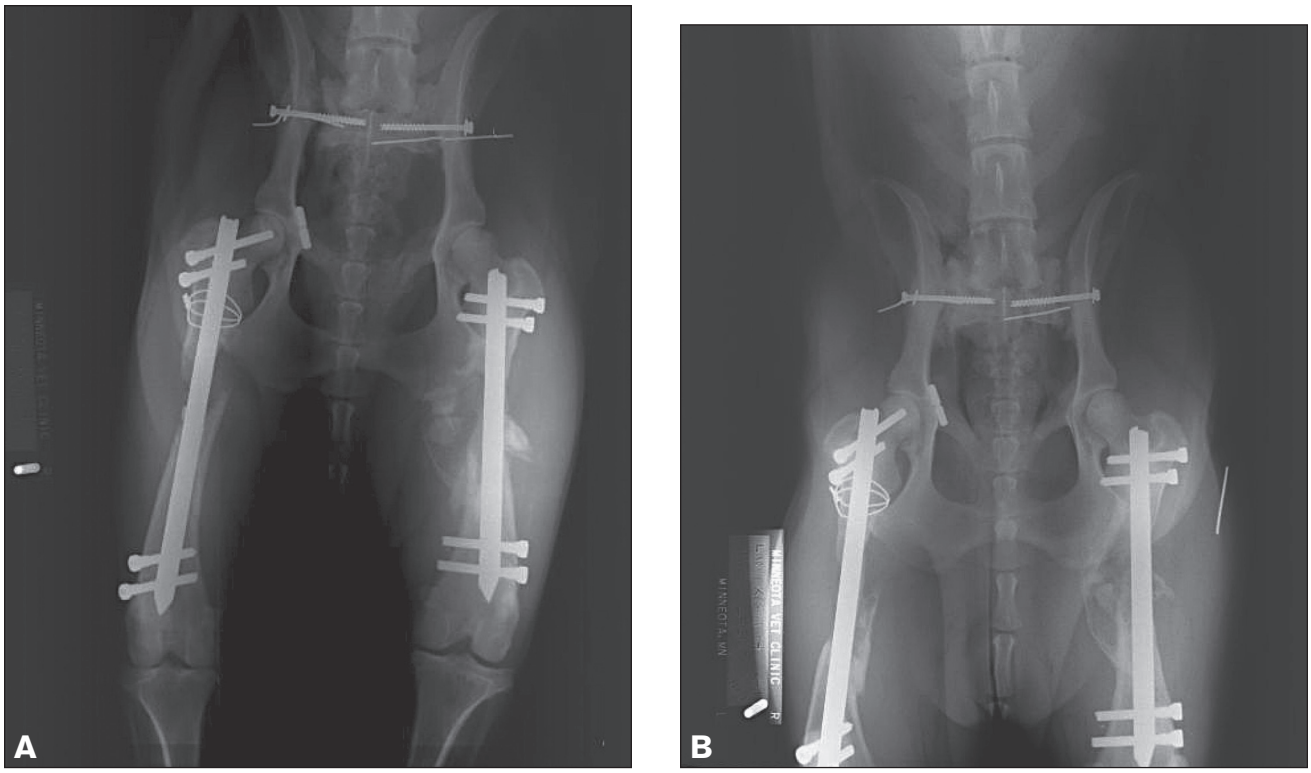

Figure 3. A. Case 13 – 0.4 mg rhBMP-2 was used to augment the repair of the left femoral fracture but not the right. B. Radiographs taken 6 wk following repair show a large bridging callus on the left and significantly less bony production on the right. Clinical function was excellent in both hindlimbs.

1 intact female (FI), and 2 FS, a MN dog, and a MI cat. All of the fractures in the healing compromised cases were treated with rhBMP-2/ACS.

Cases 9 and 10 are examples of the use of rhBMP following failure of original fixation in the short-term postoperative period. The dog in case 9 had a closed spiral tibial fracture that was treated by a limited open approach to align the fragments and by placement of a hybrid ESF. Some of the wires in the ring fixator broke less than a week after placement. The original repair was revised using open reduction to reduce the fracture fragments with full cerclage wires and a screw placed in lag fashion and more transfixation pins were added. Three weeks later the fracture appeared to be unstable, so more rings and connecting bars were added to increase the construct stiffness and strength. One week later, fresh autogenous corticocancellous bone and 0.4 mg of a 0.5-mg/mL solution of rhBMP-2 on an ACS were placed at the fracture site to help speed bone healing in this very active dog. Extensive periosteal proliferation and bridging callus consistent with a healed fracture were seen on radiographs107 d later. No adverse reactions to the BMP were noted and the fixator was removed 2 wk after the final radiographs.

The German shepherd dog in case 10 had a cranial cruciate ligament rupture treated by tibial plateau leveling osteotomy (TPLO) using a 3.5 mm broad TPLO plate. Radiographs taken after 2 wk of physical therapy showed a fibular fracture, screw breakage, and tibial plateau collapse. The original plate was reapplied with new screws and a type IA ESF was placed on the medial aspect of the tibia, and 0.4 mg of rhBMP-2 (0.5 mg/mL solution) on an ACS was placed across the osteotomy on the caudomedial cortex. Osteomyelitis with significant lysis and remodeling of the tibial plateau that developed was managed with long-term oral antibiotics. Approximately 15 wk after the revision and BMP placement, there was callus formation at the osteotomy site, but the external fixator was not removed for another 5 mo.

Cases 11, 12, and 13 are examples of repairs in which rhBMP was used at the time of initial stabilization in an attempt to assist in fracture healing. In case 11, a severe degloving wound of the left distal hindlimb and comminuted fractures of the distal tibia, talus, and calcaneus were initially treated with external coaptation. After 9 d of wound debridement and external coaptation, a pantarsal arthrodesis was performed using a circular fixator. Autogenous corticocancellous bone graft was packed into the joint after cartilage debridement and an ACS with 0.4 mg rhBMP-2 (0.5 mg/mL solution) was placed around the arthrodesis site. The dog developed severe urethral obstruction secondary to pelvic injuries 6 wk later and was euthanized. Radiographs taken at the time of euthanasia showed stable implants and evidence of bone fusion.

Case 12 was a cat with a closed comminuted humeral fracture that was reduced and stabilized with a bone plate placed on the lateral cortex as a buttress plate due to a large gap in the trans cortex. Morsellized cortical bone graft was placed in the fracture gap and ACS with 0.4 mg rhBMP-2 was placed over the fracture site to speed bone healing. Accelerated bone healing was desired to decrease the chance of implant failure from cyclic loading and collapse of the fracture gap. The fracture healed without

complication; bridging callus was seen on radiographs taken 12 wk after surgery (Figure 2).

The Labrador retriever in case 13 sustained bilateral femoral fractures, bilateral sacroiliac (SI) luxation, and right coxofemoral luxation from vehicular trauma. All of the injuries to the right hemipelvis were repaired in 1 day. The SI luxation was stabilized with a lag screw and Kirschner wire, the coxofemoral luxation was reduced and stabilized with a toggle rod and the oblique femoral fracture was stabilized with full cerclage wires and an interlocking nail augmented with autogenous corticocancellous bone graft from the right ilium. The left SI luxation and more comminuted left femoral fracture were repaired the next day. The SI luxation was stabilized with a Kirschner wire and screw placed in lag fashion and the femoral fracture was repaired with an interlocking nail augmented with autogenous corticocancellous bone graft from the left ilium and 0.4 mg rhBMP-2/ACS. Some callus was seen on the right femoral fracture, but exuberant bridging callus with evidence of remodeling of left femur was seen on radiographs taken 16 wk after surgery (Figure 3). The dog was doing well with the owner reporting excellent function of both hind limbs at that time.

Discussion

A series of 13 cases in which rhBMP-2 or rhBMP-7/OP-1 was used as an adjunct to bone healing is described. Bone morphogenetic protein may accelerate bone union in cases of open or highly comminuted fractures that are stabilized with ESF or are at high risk for delayed or non-union. The cases in our series included 3 open fractures and 3 fractures with concurrent osteomyelitis. Bone union has been reported with the use of rhBMP-2 despite the presence of osteomyelitis in 1 dog (3) and during the treatment of 14 cases of pyogenic vertebral osteomyelitis in humans (10). Humans who had rhBMP-2 supplementation in a large prospective, randomized, multi-center study to examine rhBMP-2 in fresh open tibial fractures had faster bone and soft tissue wound healing and a lower infection rate compared to individuals who did not get rhBMP-2 (11).

External skeletal fixation was used in 5 of the 13 cases in this series that ultimately resulted in bony union. This occurred despite evidence that using ESF to treat some fractures may result in a slow rate of healing and complications. Distal tibial fractures stabilized with external fixation in humans are known to heal slowly despite the use of autografts (1). Supplementing these fractures with rhBMP-7 significantly shortened healing time and time to removal of the fixator (1). In the veterinary literature, 50% of the delayed union cases reported by Milovancev et al (3) and 50% of nonunion cases reported by Schmokel et al (8) had initially been stabilized with external skeletal fixation (3,8).

Case 6 represents a rarely reported use of rhBMP for osteogenesis at a fracture stabilized with external coaptation only. While fracture stability is necessary for fracture healing, it appears that the addition of rhBMP may promote sufficient callus formation to offset delayed healing that may occur with inherent splint instability. Radiographic bone union within 24 wk may represent an expected time course for fracture healing regardless of the method of stabilization (12). The rhBMP-2 used in case 6 was placed through a small stab incision after mixing with demineralized bone matrix as a carrier. Demineralized bone matrix increases the molecular activity and decreases the solubility of rhBMP by increasing retention at the wound site, and represents an acceptable alternative to a collagen sponge that is easier to implant through a small incision approach (13).

None of the animals in this case series developed systemic adverse effects of the application of rhBMP. This is not surprising, since reports of side effects are rare despite extensive clinical use in humans (14). Potential adverse effects of rhBMP use include excess bone formation if too high a dose is used or the protein dissipates away from the graft site (15) and stimulation of malignancies if it is used in the vicinity of tumors and their metastases (16). Excessive bone formation can be especially problematic in certain sites such as periarticular areas or sites of recent spinal decompression. Irrigation of the surgical site should be avoided and hemostasis should be meticulously maintained after rhBMP implantation to avoid dispersion of the product from the primary site (14,17).

In theory, the greatest advantage of rhBMP use is that there is no need to harvest and use autogenous cancellous bone graft. Using a recombinant product such as rhBMP in lieu of autogenous bone grafts avoids the need for additional anesthetic time or personnel needed for graft harvesting and the potential for an insufficient quantity of graft, limited access to donor sites, loss of osteogenic cells, donor site pain or hemorrhage, and failure of the donor bone (16). In the case series presented here, 8 of the 13 animals had concurrent or previous cancellous grafting. Similarly, in a human clinical trial, patients with recalcitrant, atrophic, aseptic long bone non-unions had undergone an average of 2.1 procedures and nearly half (28/62) of the fractures had not healed despite autogenous iliac crest bone grafting. After treatment with a standard protocol that included hardware removal/deformity correction when necessary, rigid stabilization, and placement of an OP-1 implant, 89% of the non-unions progressed to heal (18).

The rhBMP was used in 8 cases with delayed or non-union in this report. In these cases, bony union had progressed at a rate that was slower than expected. In the remaining 5 cases, however, it was the judgment of the attending clinician that an adjunct therapy was necessary to maximize the chances of a bony union. These decisions were driven by the clinician's previous experience and the clinical circumstances. There are no controls for comparison of the outcome in these cases and the injuries may have healed without the benefit of rhBMP.

There are several limitations of this study; it is retrospective and the BMP was used in a non-random manner. The follow-up examinations were carried out at varying time intervals and by referring veterinarians, limiting the usefulness of objective scoring of lameness/gait or radiographic healing. However, this report does describe a wide variety of cases using both OP-1 and rhBMP-2 to successfully promote bone healing. The use of BMPs in veterinary medicine may soon become more widespread as a veterinary product has been developed and undergone a large, prospective randomized, controlled clinical trial. Although the results of this study are not yet available, the product should be ready for marketing in the near future.

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